

CLAIMS

1. An aqueous solution suitable for intranasal administration, which comprises from 0.1 to 10 mg/ml of buprenorphine or a physiologically acceptable salt or ester thereof and from 5 to 40 mg/ml of a pectin having a degree of esterification of less than 50%; which solution has a pH of from 3 to 4.2, is substantially free from divalent metal ions and gels on the nasal mucosa.
2. A solution according to claim 1, wherein the buprenorphine or buprenorphine salt or ester is present in an amount of from 0.5 to 8 mg/ml.
3. A solution according to claim 2, wherein the buprenorphine or buprenorphine salt or ester is present in an amount of from 1 to 6 mg/ml calculated as buprenorphine.
4. A solution according to any one of the preceding claims, which comprises buprenorphine hydrochloride.
5. A solution according to any one of the preceding claims, wherein the pectin is present in an amount of from 10 to 30 mg/ml.
6. A solution according to any one of the preceding claims, wherein the pectin has a degree of esterification of from 10 to 35%.
7. A solution according to any one of the preceding claims, wherein the pH is from 3.5 to 4.0.
8. A solution according to any one of the preceding claims, wherein the pH has been adjusted by means of hydrochloric acid.
9. A solution according to any one of the preceding claims, which comprises a preservative.
10. A solution according to claim 9, which comprises phenylethyl alcohol and propyl hydroxybenzoate as preservatives.
11. A solution according to any one of the preceding claims, which has an osmolality of from 0.35 to 0.5 osmol/kg.
12. A solution according to any one of the preceding claims, which contains dextrose as a tonicity adjustment agent.

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13. An aqueous solution suitable for intranasal administration, which has a pH of from 3.5 to 4.0, which is substantially free from divalent metal ions and which comprises:

- (a) from 1 to 6 mg/ml of buprenorphine or a physiologically acceptable salt or ester thereof, calculated as buprenorphine,
- (b) from 10 to 40 mg/ml of a pectin which has a degree of esterification from 10 to 35%, and
- (c) dextrose as a tonicity adjustment agent.

14. A process for the preparation of an aqueous solution as defined in claim 1, which process comprises dissolving buprenorphine or a physiologically acceptable salt or ester thereof in water; mixing the resulting solution with a solution in water of a pectin having a degree of esterification of less than 50% such that the mixed solution comprises from 0.1 to 10 mg/ml of buprenorphine or said salt or ester thereof and from 5 to 40 mg/ml of the pectin; and adjusting the pH of the solution to a value from 3 to 4.2 if desired.

15. A process according to claim 14, wherein the resulting solution is introduced into a nasal delivery device.

16. An aqueous solution suitable for intranasal administration, which comprises:

- (a) from 0.1 to 10 mg/ml of buprenorphine or a physiologically acceptable salt or ester thereof,
- (b) from 0.1 to 20 mg/ml of a chitosan, and
- (c) from 0.1 to 15 mg/ml of hydroxypropylmethylcellulose;

which solution has a pH of from 3 to 4.8.

17. A solution according to claim 16, wherein the hydroxypropylmethylcellulose has an apparent viscosity of from 3000 to 6000 cps and is present in an amount of from 0.1 to 15 mg/ml.

18. A solution according to claim 17, wherein the hydroxypropylmethylcellulose is present in an amount of from 0.5 to 10 mg/ml.

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19. An aqueous solution suitable for intranasal administration, which comprises:

- (a) from 0.1 to 10 mg/ml of buprenorphine or a physiologically acceptable salt or ester thereof,
- (b) from 0.1 to 20 mg/ml of a chitosan, and
- (c) from 50 to 200 mg/ml of a polyoxyethylene-polyoxypropylene copolymer of the general formula $\text{HO}(\text{C}_2\text{H}_4\text{O})_a(\text{C}_3\text{H}_6\text{O})_b(\text{C}_2\text{H}_4\text{O})_a\text{H}$ wherein a is from 2 to 130 and b is from 15 to 67;

which solution has a pH of from 3 to 4.8.

20. A solution according to claim 19, wherein the polyoxyethylene-polyoxypropylene copolymer is present in an amount of from 80 to 120 mg/ml.

21. A solution according to claim 19 or 20, wherein the polyoxyethylene-polyoxypropylene copolymer has a molecular weight of from 7,000 to 15,000.

22. A solution according to any one of claims 19 to 21, wherein the polyoxyethylene-polyoxypropylene copolymer is one in which a is 80 and b is 27.

23. A solution according to any one of claims 16 to 22, which has an osmolality of from 0.32 to 0.4 osmol/kg.

24. A solution according to any one of claims 16 to 23, wherein the buprenorphine or buprenorphine salt or ester is present in an amount of from 0.5 to 8 mg/ml.

25. A solution according to claim 24, wherein the buprenorphine or buprenorphine salt or ester is present in an amount of from 1 to 6 mg/ml calculated as buprenorphine.

26. A solution according to any one of claims 16 to 25, which comprises buprenorphine hydrochloride.

27. A solution according to any one of claims 16 to 26, wherein the chitosan is present in an amount of from 2 to 10 mg/ml.

28. A solution according to any one of claims 16 to 27, wherein the chitosan is a physiologically acceptable salt of a deacetylated chitin

29. A solution according to claim 28, wherein the salt is chitosan

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glutamate.

30. A solution according to any one of claims 16 to 29, wherein the pH is from 3.5 to 4.0.

31. A solution according to any one of claims 16 to 30, wherein the pH has been adjusted by means of hydrochloric acid.

32. A solution according to any one of claims 16 to 31, which comprises a preservative.

33. A solution according to claim 32, wherein the preservative is benzalkonium chloride.

34. A solution according to any one of claims 16 to 33, which contains dextrose as a tonicity adjustment agent.

35. A process for the preparation of an aqueous solution as defined in claim 16, which process comprises dissolving buprenorphine or a physiologically acceptable salt or ester thereof, a chitosan and hydroxypropylmethylcellulose in water to provide a solution comprising from 0.1 to 10 mg/ml of buprenorphine or said salt or ester thereof, from 0.1 to 20 mg/ml of the chitosan and from 0.1 to 15 mg/ml of hydroxypropylmethylcellulose; and adjusting the pH of the solution to a value from 3 to 4.8 as desired.

36. A process for the preparation of an aqueous solution as defined in claim 19, which process comprises dissolving buprenorphine or a physiologically acceptable salt or ester thereof, a chitosan and a polyoxyethylene-polyoxypropylene copolymer of the general formula $\text{HO}(\text{C}_2\text{H}_4\text{O})_a(\text{C}_3\text{H}_6\text{O})_b(\text{C}_2\text{H}_4\text{O})_a\text{H}$ wherein a is from 2 to 130 and b is from 15 to 67 in water to provide a solution comprising from 0.1 to 10 mg/ml of buprenorphine or said salt or ester thereof, from 0.1 to 20 mg/ml of the chitosan and from 50 to 200 mg/ml of the polyoxyethylene-polyoxypropylene copolymer; and adjusting the pH of the solution to a value from 3 to 4.8 as desired.

37. A process according to claim 35 or 36, wherein the resulting solution is introduced into a nasal delivery device.

38. A nasal delivery device loaded with a solution as claimed in any one of claims 1 to 13 or 16 to 34.

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39. A device according to claim 38, which is a spray device.
40. Use of a solution as defined in any one of claims 1 to 13 or 16 to 34 for the manufacture of a nasal delivery device for use in inducing analgesia.
41. A method of inducing analgesia in a patient in need thereof, which method comprises intranasally administering an aqueous solution as defined in claim 1, 16 or 19 to the patient.
42. Use of buprenorphine or a physiologically acceptable salt or ester thereof and a delivery agent for the manufacture of a medicament for administration intranasally for the treatment of pain whereby, on introduction into the nasal cavity of a patient to be treated, the buprenorphine or salt or ester thereof is delivered to the bloodstream to produce within 30 minutes a therapeutic plasma concentration C_{ther} of 0.4 ng/ml or greater which is maintained for a duration T_{maint} of at least 2 hours.
43. Use according to claim 42, wherein the medicament is an aqueous solution.
44. Use according to claim 42 or 43, wherein the delivery agent is a pectin having a degree of esterification of from 10 to 35%.
45. Use according to any one of claims 42 to 44, wherein C_{ther} is from 0.4 to 1 ng/ml and is produced within 1 to 15 minutes.
46. Use according to any one of claims 42 to 45, wherein C_{max} is from 1 to 5 ng/ml and is reached 10 to 30 minutes after introduction of said medicament into the nasal cavity of a patient to be treated.
47. Use of a pharmaceutical composition which comprises buprenorphine or a physiologically acceptable salt or ester thereof and a delivery agent for the manufacture of a nasal delivery device for use in inducing analgesia whereby, on introduction into the nasal cavity of a patient to be treated, the buprenorphine or salt or ester thereof is delivered to the bloodstream to produce within 30 minutes a therapeutic plasma concentration C_{ther} of 0.2 ng/ml or greater which is maintained for a duration T_{maint} of at least 2 hours.
48. A pharmaceutical composition suitable for use as an analgesic which comprises buprenorphine or a physiologically acceptable salt or ester thereof and a

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delivery agent whereby, on introduction into the nasal cavity of a patient to be treated, the buprenorphine or salt or ester thereof is delivered to the bloodstream to produce within 30 minutes a therapeutic plasma concentration C_{ther} of 0.2 ng/ml or greater which is maintained for a duration T_{maint} of at least 2 hours.

49. A method of inducing analgesia in a patient in need thereof, which method comprises administering intranasally to said patient a pharmaceutical composition which comprises buprenorphine or a physiologically acceptable salt or ester thereof and a delivery agent whereby, on introduction into the nasal cavity of said patient to be treated, the buprenorphine or salt or ester thereof is delivered to the bloodstream to produce within 30 minutes a therapeutic plasma concentration C_{ther} of 0.2 ng/ml or greater which is maintained for a duration T_{maint} of at least 2 hours.

50. A method according to claim 49, wherein a unit dosage of 0.1 to 0.6 mg of buprenorphine or buprenorphine salt or ester, calculated as buprenorphine, is administered intranasally.